International Formula Council

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Re: Written comments on the NTP Final CERHR Expert Panel Report on Soy Formula

Dear Dr. Thayer:

These comments are submitted on behalf of the International Formula Council (IFC)[*], an association of manufacturers and marketers of formulated nutrition products, e.g., infant formulas and adult nutritionals, whose members are based predominantly in North America.

We wish to make the following observations and comments on the January 15, 2010 NTP Final CERHR Expert Panel Report on Soy Formula.

As manufacturers of infant formula, we understand that our products often provide sole source nutrition at a critical time for growth and development. Thus, we continually work to assure our formulas are safe and of the utmost quality. Infant formula is one of the most highly regulated food products in the U.S. Through ongoing clinical research and routine review and evaluation of the scientific literature, we also work to assure that our products reflect the latest nutrition advances. We take very seriously all issues related to the safety and efficacy of our products.

It is from this perspective that we once again bring forward our concerns expressed in previous comments dated June 11, 2004, March 1, 2006, June 30, 2006, and December 8, 2006 made during the 2006 NTP-CERHR investigation of the safety of soy formula, and our most recent comments made December 3, 2009 on the latest Expert Panel Draft Report. **The safety of soy-based infant formulas (SIF) has been adequately addressed in previous reviews and the weight of scientific evidence in new research continues to uphold SIF safety**.

From our ongoing review of the scientific evidence and our review of the January 15, 2010 Expert Panel Final Report, we believe that there is no new information that provides sufficient justification for a reevaluation of SIF safety. We reaffirm our position that SIF safely provide necessary and appropriate nutrition for normal growth and development in term infants. This view is consistent with that expressed more than a decade ago by the 1997 National Institutes of Health/U.S. Food and Drug Administration (FDA) Panel Meeting on the significance of phytoestrogens in SIF. It is also supported by the 2008 position of the American Academy of Pediatrics (AAP) that the use of SIF is a safe and effective alternative to provide appropriate nutrition for normal growth and development in term infants.

We make reference to, but will not repeat, the extensive evidence supporting the safe use of SIF provided in our December 3, 2009 comments. We remind CERHR that for almost half a century modern SIF have been fed safely to over 25 million American infants. These formulas are commonly

[*] IFC members are: Abbott Nutrition; Mead Johnson Nutritionals; Nestlé Infant Nutrition; and Pfizer Nutrition.

used to achieve successful medical outcomes in infants with IgE-mediated cow milk allergy, cow milk-based formula intolerance, lactose intolerance, galactosemia, and to provide an important infant feeding alternative as a vegetarian human milk substitute, and in observance of religious practices and traditions.

Specific Comments on the NTP Final CERHR Expert Panel Report on Soy Formula dated January 15, 2010

CHAPTER 3: DEVELOPMENTAL TOXICITY OF SOY FORMULA

Section 3.7 Conclusions

The Expert Panel Report indicates, and IFC concurs, there is sufficient evidence to conclude that high levels of genistein, by itself, produce developmental toxicity in male and female mice and rat models. However, these rodent toxicities are only seen at doses substantially higher (4 - 22 fold higher in mice and 2.7 – 44 fold higher in rats) than observed for human infants fed SIF. More significantly, there are very clear physiological differences between species. In the rodent model the predominant circulating form is unconjugated genistein, which is chemically and biologically different than the inactive conjugated forms of genistein that typically circulate in humans. IFC reminds CERHR of the March 1, 2006 comments on the 2006 Draft Expert Panel Report on Soy Formula made by Dr. Kenneth Setchell, Cincinnati Children's Hospital. Dr. Setchell provided compelling arguments that "much of what has been shown in immature and adult rodents (regarding soy formula safety) be disregarded as irrelevant to the human newborn and infant." We believe his analysis reflects the balance of current scientific evidence. We question how, given the significant physiological species differences in genistein metabolism documented in the literature, the Expert Panel reached a different conclusion, specifically that "The experimental animal data are considered relevant to the assessment of human risk."

The Expert Panel Report indicates, and IFC concurs, that evidence is insufficient to conclude that soy infant formula or other soy exposures, including soy-based diets, produces or does not produce developmental toxicity in experimental animals. However, it is important to note that outside the laboratory, the successful use of soy-based diets in hundreds of millions of commercial swine produced annually in the United States creates a very practical and strong argument for safety. This is particularly relevant because swine are now known to be the closest animal model of human isoflavone metabolism.

For human infants specifically, IFC disagrees with the Expert Panel Report's conclusion that there is insufficient evidence to conclude that soy infant formula produces or does not produce toxicity with infant exposure in girls or boys at recommended intakes (as manifested by the following endpoints: bone mineral density, gastrointestinal effects, allergy/immunology, thyroid function, reproductive endpoints, cholesterol, diabetes mellitus, and cognitive function). IFC believes that there is in fact substantial human infant data showing no toxicity. We disagree with the Expert Panel Report's interpretation of the data and find their analysis incomplete. In particular, we question how <u>any</u> clinical study involving trained medical observation of infants fed SIF in a controlled setting can be judged as providing "no utility" in assessing the developmental toxicity of SIF. Yet the Expert Panel Report judges 44 of the 70 human studies evaluated (62%) to be of "no utility". The remaining 26 studies were designated to be of "limited utility" and none of the human studies were judged to be of "high utility". IFC reminds CERHR that the vast majority of these clinical studies were published in peer-reviewed scientific journals, all were approved by Internal Review Boards / human subject use committees, and most were funded through highly competitive Federal grants. We find the Report's conclusion of "insufficient evidence" unsubstantiated when the Report classifies published studies involving more than 7,600 patients as providing "no utility" in addressing human developmental toxicity. Finally, as shown in IFC's December 3, 2009 comments, that there are a number of important clinical studies in the literature that are not reviewed in the Expert Panel Report.

The Expert Panel Report indicates, and IFC concurs, that evidence is sufficient to conclude that use of soy infant formula in healthy full-term infants does not impair growth during infancy. IFC and the pediatric medical and regulatory communities view infant rate of growth data as a key overall indicator of the nutritional value of an infant feeding system. The clear equivalence of infant growth seen in studies of SIF is a powerful statement that these formulas support normal infant development.

CHAPTER 4 SUMMARY

Section 4.1 Summary of Human Exposure

The Expert Panel Report includes an extensive review of human infant exposure to the dietary isoflavones present in SIF. Data contained in the Report seem to accurately estimate total isoflavone intake by U.S. infants fed SIF at 2.3 – 9.3 mg/kg bw/day (estimated intake for genistein, expressed in aglycone equivalents, ranges from 1.3 to 6.2 mg/kg bw/day), depending on age of the infant. It is critical to use these estimates of isoflavone intake as a benchmark when assessing the relevance of animal experiments. As discussed previously, many studies with experimental animals reviewed in the report evaluated the impact of isoflavone "doses" substantially above this range.

IFC notes that the Report focuses nearly exclusively on potential reproductive and developmental toxicity associated only with isoflavones contained in SIF. Further, the Report appears to consider all modern soy-based formulas to be equivalent. While this may be reasonable for isoflavone content, it is not true for the many other components that distinguish these formulas. Compositional and nutritional performance differences are known to exist among available SIF. This represents a confounding element in the analysis of clinical data that has not been included in the Expert Panel Report's assessments.

The Expert Panel Report indicates, and IFC concurs, that the degree to which infants are exclusively fed soy formula versus a combination of soy and non-soy formula and/or breast milk is not clearly known. Exposure to soy formula also varies depending on developmental stage (*e.g.*, weaning), and cultural variations in soy formula and soy product usage are known to exist.

IFC confirms that SIF sales (and approximate proportion of infant formula servings fed) represent approximately 12% of U.S. infant formula consumption, and that this number has declined by approximately 50% over the last 10 years.

The Expert Panel Report lists the guidelines on soy formula use by AAP and ESPGHAN that do not recommend SIF use to manage cow milk-allergic infants, but the report fails to mention in the summary recommendations from the Australian Consensus Panel (EP Reference 275) that indicate, "SIF is the first choice for managing infants over 6 months of age with immediate (IgE-mediated) food reactions, and for those with gastrointestinal symptoms or atopic dermatitis in the absence of failure to thrive."

The Expert Panel Report indicates that the geometric mean value of total blood genistein in infants fed soy infant formula is 757 ng/ml (75th percentile value for total blood genistein is 1455 ng/ml). Since most isoflavones in human circulation are inactive conjugates (estimated @ >80%) this suggests that animal experiments targeting isoflavone aglycone serum concentrations of greater than 300 ng/mL are not likely to be relevant to human toxicity. This standard has clearly not been applied to the Report's analysis of the animal data.

Section 4.2 Summary and Conclusions of Pharmacokinetics

This section of the Expert Panel Report is confusing and difficult to interpret. The first paragraph indicates that there are no pharmacokinetic data for individual isoflavones and no estimates of variability in exposure to individual isoflavones (genistein, daidzein, equol and glycitein), or pharmacokinetic parameters describing the disposition of those isoflavones following administration of soy-based infant formula to infants or children. The Report concludes that reliable estimates of exposure, as defined by area under the plasma concentration-time curve (AUC), are not available and therefore preclude meaningful comparisons of exposure between infants receiving recommended intakes on normal feeding schedules and experimental animal models. To resolve this issue the report recommends that, given the heterogeneity of the human infant population, population studies incorporating measures of systemic exposure (i.e., accurately timed plasma samples and quantitative urinary recoveries) are essential to identify a potentially susceptible subgroup, if one exists. IFC is unaware of any data in the literature indicating a substantial and medically significant heterogeneity in the metabolic pathways of isoflavones in human infants and thus questions the ethical justification and cost/benefit value of a study large enough to effectively address this issue.

The second paragraph seems to argue that significant amounts of unconjugated genistein are or could be present in infant circulation following SIF consumption, and that the unconjugated form would play a significant role in infant isoflavone reactivity. This seems logical since the unconjugated form is the only one with estrogen receptor binding reactivity, but in fact most of the genistein in infant circulation following SIF intake is in the inactive conjugated form. The report seems to weaken the argument that when comparing human data to animal models it is imperative to adjust the animal (especially the rodent) aglycone dose downward to compensate for the fact that most of the isoflavones in human fluids are in the inactive conjugated forms. This is a critical component of interpreting the significance of the animal data, yet, for the most part, these adjustments are not included in the Report's assessment of the animal studies.

The Report's comments on equol: "Equol exposure in human infants following daidzein intake is relatively low compared to animals of a comparable developmental stage. This observation is relevant for the risk assessment of daidzein, but not of importance to the risk assessment of soy formula due to the detection of equol in infants independent of feeding type." This position misses the point that the production of equol (with its higher estrogenic potential versus daidzein) by animals in the studies reviewed increases the potential estrogen receptor effects in the animals compared to non equol-producing human infants.

Section 4.3 Summary and Conclusions of Developmental Hazards

Section 4.3.1 Humans

As indicated above, IFC concurs with the Expert Panel Report's assessment that SIF support normal growth in healthy term infants, and disagrees with the Reports conclusion of insufficient evidence to assess whether SIF produces developmental toxicity with infant exposure in girls or boys at recommended intake levels. IFC recognizes the potential limitations related to the several problems of clinical trial design as listed in this section of the Report, but rejects the conclusion that the presence of one or more of these design shortcomings (which are often typical in human infant nutrition studies) renders all study data as providing "no utility" in addressing the larger issue of SIF developmental toxicity. IFC also is disappointed to note, as we have stated several times previously, the continued absence of any consideration of or recommendation for History of Safe Use studies of SIF.

IFC comments on selected Expert Panel remarks in this Section:

The comment, "Limited retrospective data suggest that soy formula fed infants may demonstrate premature thelarche (the start of breast development at the beginning of puberty) [576]." is an incomplete and incorrect assessment of the experience in Puerto Rico. IFC notes that, in spite of our 2006 comments on this subject, the Expert Panel Report does not list the publication by Colon et al. (Colon, I., Caro, D., Bourdony, C.J., Rosaro, O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ. Health Perspect. 2000; 108(9): 895-900) identifying environmental phthalates as the probable cause of the Puerto Rican premature thelarche.

In our June 30, 2006 letter to CERHR addressing the 2006 Expert Panel Final Report IFC comments:

" *"Another case-control study to examine premature breast development in females and exposure to soy infant formula is needed."*

This recommendation is presumed to be triggered by the Freni-Titulare et al. study (Expert Panel Report, reference 162). This study describes a substantial increase in rates of premature thelarche in Puerto Rican children. This is a public health anomaly isolated to Puerto Rico that has been followed since 1978. In a subset of patients, soy formula use was associated with premature thelarche with an odds ratio of 2.2, (90% CI = 1.0-5.2. P = 0.05). However, in the same study, chicken consumption showed a premature thelarche odds ratio of 4.9 (95% CI = 1.1-21.9, P = 0.039). The authors indicated that their multivariate analysis showed no significant associations overall. They also noted that in more than 50% of the thelarche patients, there was no exposure to any of the risk factors (including soy formula consumption) for which statistical associations were found. Monitoring of premature thelarche in Puerto Rico has continued. By 1995, Puerto Rico's Premature Thelarche and Precocious Sexual Development Registry contained 2,716 case reports. Analyses of these data by Colon et al. (6) showed the incidence of premature thelarche in Puerto Rico was 10-15 times the rate in "Olmsted, Minnesota" (note that the soy infant formulas used in Puerto Rico are typically the same brands and have the same compositions as those used the United

States). These authors also reported that serum samples of most (68%) thelarche patients contained endocrine-disrupting phthalates, presumed to be from the local environment. IFC believes that the premature thelarche seen in Puerto Rico is an isolated public health problem, is not reproduced in like-fed U.S. populations, and has nothing to do with use of soy infant formulas. We also note that the increase in premature thelarche incidence was quickly identified by the normal health care delivery system as a serious problem. If a similar problem appeared in the United States, it also would be rapidly identified. At least in Olmsted, this was not the case. Taken as a whole, these data do not justify funding new clinical studies to examine premature breast development in females exposed to soy infant formula. Concern about this issue could be fully addressed by a HOSU analysis.

Failure to identify this important study by Colin et al and to fully consider it in interpreting the preliminary and confusing reports from Puerto Rico is of great concern, especially given the significance attributed to the Freni-Titulare et al. study in Section 4.4 Overall Conclusions, page 725, bullet point 4.

Section 4.3.2 Experimental Animals

In view of the wealth of human clinical data readily available, the 50 year history of successful use of soy formula in more than 25 million American infants, and the questions raised previously regarding the relevance of data from experimental animal trials, IFC questions the value of the Expert Panel Report's emphasis using mostly experimental animal data to assess the developmental toxicity of SIF in human infants. As indicated earlier, our position on the use of these animal models is reasonably summarized in Dr. Kenneth Setchell's March 1, 2006 comments on the 2006 Draft Expert Panel Report on Soy Formula. We realize that this is not the position of CERHR and note that approximately 169 studies describing animal model results were reviewed in the Expert Panel Report. Of these studies 34.9% were rated as of "no utility," 61.5% were rated "limited utility," and 3.6% (6 studies) were rated as "high utility." In contrast, of the 70 human clinical studies reviewed in the Expert Panel Report, 63% were rated as of "no utility," 37% were rated "limited utility," and none were rated "high utility." We urge CERHR to consider the implications of this comparison in assessing the balance and value of the opinion expressed in the Expert Panel Report.

Section 4.4 Overall Conclusions

It is the opinion of IFC that the Expert Panel Report's conclusion of "minimal concern" for adverse developmental effects in infants fed soy infant formula is not supported by the whole of the available data and that a finding of "negligible concern" more accurately represents the data and the actual SIF clinical feeding experience.

Bullet points 1-3 pertain to flawed animal model data and should not be a factor in developing the final recommendation.

Bullet point 4 identifies "a number of studies in experimental animals" and "one study in humans" as the drivers for elevating the level of concern from negligible to minimal. The new details of the Puerto Rican premature thelarche experience presented above should remove this human study as a negative factor thereby eliminating any human data as a driver for the recommendation.

Bullet point 5, "Studies of sufficient quality in humans have not been conducted to address the concerns raised from the experimental animal findings or to identify previously unrecognized endpoints." is not supported by the balance of published science or practical experience. Specifically, the Expert Panel Report's review of the clinical literature is incomplete and dismisses many relevant studies. Also, given the ability of the current public health care system to identify a small population of premature thelarche patients in Puerto Rico, in comparison to over 25 million American infants fed modern soy formulas, it is highly unlikely that previously unrecognized SIF toxicity endpoints could still exist.

In the final IFC analysis, the Expert Panel Final Report conclusion of minimal concern instead of negligible concern is based on an incorrect assessment of flawed experimental animal data and an incomplete analysis of the body of evidence of human clinical data and SIF feeding history.

Section 4.5 Critical Data Gaps and Research Needs

4.5.1 Pharmacokinetics

IFC sees little practical value and substantial ethical and logistic concerns in addressing any of the stated knowledge deficits and research needs listed in this section.

4.5.2 Human Epidemiological

This section asks some interesting questions. However, IFC is concerned that none of the questions can be answered in a reasonable time frame or for a practical cost. The execution of a randomized, blinded prospective study with thousands of SIF and control-fed patients measuring developmental and reproductive endpoints is a truly daunting task. A primary reproductive outcome for such a study would be fertility. Complete understanding of potential fertility effects could take at least fifty years, with inestimable costs. It is for these reasons that IFC has continued to recommend conducting retrospective research on the large numbers of infants fed SIF over the past 50 years. It is disappointing that the Expert Panel Report again fails to include any recommendation for retrospective or history of safe use research.

4.5.3 Experimental Animal

IFC recommends that any further animal studies be restricted to trials in pigs fed soy formulas, because of the similarity between swine and human metabolism of soy products. IFC also recommends that the literature describing the use of soy in swine nutrition should be carefully reviewed from a developmental and reproductive safety perspective.

Summary of IFC Comments

As stated earlier, we take very seriously all issues related to the safety and efficacy of our products. Our conclusions today are essentially the same as in 2006 because the weight of scientific evidence has not changed: the general safety of soy-based infant formulas in term infants, at levels commonly consumed, has been comprehensively and unequivocally established. There is no valid clinical data (either historical or new) indicating reproductive or developmental toxicity of soy-based infant formulas. Artificial laboratory animal models testing dietary components outside a food (formula) matrix, in species with isoflavone metabolism grossly different than humans, with inappropriately high doses, and by non-dietary exposure routes offer no public health benefit in the understanding of practical food toxicology, and should not be supported through continued governmental funding.

Soy-based infant formulas safely provide appropriate nutrition for normal growth and development in term infants and give parents and health care professionals an important and sometimes critical infant feeding option. If parents are unnecessarily alarmed about the safety of feeding soy infant formulas, they may choose to feed something else that is proven neither safe nor nutritious and thus not in the best interest of their infants.

The IFC appreciates the opportunity to comment on the 2010 Final CERHR Expert Panel Report on Soy Infant Formula.

Respectfully submitted,

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Executive Vice President